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Headache

Pharmacological Approach to Treatment

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• **The great majority of headaches a physician treats in office practice can be divided into two main categories, muscular contraction headache of tension type and vascular headaches of the migraine type.**

The most satisfactory symptomatic therapy for tension headache is by the use of a nonnarcotic analgesic agent combined with a tranquilizer or sedative. On the other hand, symptomatic relief of migraine is best obtained by the use of a suppository of ergotamine tartrate and caffeine combined with an antiemetic or antispasmodic.

Interval treatment of patients with tension and migraine headache centers on helping the patient understand his emotional problems. Prophylactic drug therapy for patients with tension headache includes the limited use of tranquilizers and sedatives. Recently, striking benefits in some patients with migraine have been achieved by the prophylactic use of the antiserotonin drug methysergide (UML 491).

MORE DRUGS for the treatment of headache have become available to physicians in the past ten years than in all the previous history of American medicine. This flood of new drugs has resulted from progress in pharmacological research and from increased knowledge of the basic mechanisms of head pain. Yet from a critical review of the literature it appears that the number and the effectiveness are not closely related. On the contrary, the very fact that more than 400 drugs have been offered for the treatment of migraine seems more a measure of shortcomings than of succcessful therapy.

The purpose of this presentation is (1) to consider criteria and basic principles for clinical evaluation of drugs and (2) to evaluate some of the drugs recently introduced in the treatment of vascular and muscular contraction headaches, which constitute over 90 per cent of the headaches the physician will treat in his office.

Criteria and Basic Principles

In evaluating the treatment of headache by pharmacological methods, a number of factors are difficult to control. Headache as a symptom is a subjective response, evident only to the individual experiencing it. The appraisal of therapy depends upon a cooperative statement made by the subject. Moreover, there are three areas in which effect of the drug must be considered: (1) The original pain sensation and its mechanism; (2) the anxiety associated with the pain, and (3) the secondary increase in dysfunction, including the additional pain sensation which accompanies the anxiety.

Response to any therapy will be affected by the patient-physician relationship. In my experience, the pharmacological effect of sedatives, tranquilizers and analgesics is decidedly influenced by the

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physician's ability to relieve the patient's anxiety. Response to a remedy also depends upon the psychological status of the patient, whose attitude may range from constructive to cynical. The physician's attitude toward the drug being administered influences the results: the therapeutic enthusiast always does better than the therapeutic nihilist. It also must be emphasized that the physician's understanding of the pharmacologic action of the drug being used, including such parameters of a drug as mode of administration, dosage, number of doses and frequency of administration have pronounced effect on the results of treatment.

Unfortunately the observations made by inducing headache for experimental purposes and then appraising the results of chemical agents on the symptoms, are not as reliable as observations of the treatment of spontaneous headache. Consequently, despite the difficulties, clinical use in the treatment of patients is the only way to make a valid test of the value of any drug in the treatment of headache.

Method of Drug Evaluation

Evaluation of both symptomatic and prophylactic therapeutic agents for headache requires a comparison of groups of patients taken at random. Essential parts of the investigation are double-blind techniques including a placebo and standard drug of reference for comparison; also standardization of order, correlated data, mathematical validation of difference, and appraisal of side effects. Studies of this type are difficult from two standpoints: patient material and the investigator's time.

It is my belief that new compounds must be more than simply helpful; to be considered of real value they must prove superior to other established drugs. However, other investigators believe that any drug capable of helping in any way is valuable—this on the grounds that in many instances it is not possible to evaluate drugs under the ideal criteria but it is possible that their usefulness may be established by giving them to many patients over a long period.

Placebo Effect

In the appraisal of drugs intended to alter subjective responses such as head pain, the placebo deserves especial attention. It is important to remember that placebo effects are not imaginary, and that virtually all organs are capable of responding to placebos. The placebo derives its power from the fact that the administration of it is meaningful for the patient. Objective laboratory tests have shown that placebos can stimulate the adrenal glands and mimic drug action.[2] This action is thus not necessarily only a psychological one. It also should be emphasized that response to a placebo in one situation may be quite different from the response in another. Individual attitudes and reactions to treatment vary enormously from patient to patient and even with the same patient from time to time and cannot be precisely duplicated.

Clinical Use of Pharmacological Therapy

Headache is a symptom and not a disease. The goals in pharmacotherapy are to interrupt the mechanism that produces the pain, to raise the pain threshold and to reduce the emotional tension and anxiety responsible for or associated with the pain. Prevention of headache is difficult but control of the attack of pain is usually successful. The small minority of headaches secondary to a specific acute illness are treated through control of the primary pain and correction of the underlying disorder. The great majority of headaches are psychophysiological responses involving cranial arterial dilatation or muscular contraction without any structural changes. It is with this group that this communication deals. Management of the patient should be considered from two aspects, prophylactic and symptomatic.

Vascular Headache of the Migraine Type

Migraine is a symptom complex consisting of periodic, recurrent, commonly unilateral headache, often associated with anorexia, nausea and vomiting and having a variety of prodromal symptoms, including visual disturbances. Frequently a history of similar headache in the parents or other members of the family is noted. Although headache is the most prominent feature of migraine, the syndrome may manifest itself in widespread derangement of bodily function, including mood disturbances.[8]

The painful phase of migraine is associated with vasodilatation, during which the cranial vessels show altered sensitivity and increased amplitude of pulsation. Recent studies indicated that the sensitivity of the blood vessels is in part due to the accumulation of a substance of low molecular weight (neurokinin), which may be responsible for lowering the pain threshold.[1]

For convenience of diagnosis and treatment, migraine headaches can be divided into the following categories:[4]

(a) Vascular headache in which prodromata—visual, sensory or motor—are sharply defined neurological phenomena ("classical migraine").

(b) Vascular headache in which pronounced cephalic autonomic phenomena occur with the head pain in a cluster pattern ("cluster migraine").

(c) Vascular headache without striking prodromata and less well defined variable features ("ordinary migraine").

(d) Vascular headache accompanied by major neurological phenomena which persist during and after the headache ("ophthalmoplegic migraine," "hemiplegic migraine").

Symptomatic Treatment of Migraine

The most effective drug in the treatment of an attack of vascular headache of the migraine type is ergotamine, which provides an excellent example of affording relief for head pain without any direct analgesic effect. The beneficial effect of ergotamine administration probably depends on its action on the smooth muscles of the blood vessels, causing a constriction of these vessels, as well as on its central action. Its effectiveness in migraine therapy has further been improved by combining it with caffeine to potentiate its action and with other compounds to reduce its side effects and to control other symptoms associated with the migraine attack. Many forms of ergotamine derivatives are now available in proprietary preparations incorporating antispasmodics, sedatives and antiemetics to suit the individual patient's need. The drug can be given by inhalation or by sublingual, oral, rectal or parenteral routes. In ordinary and classical migraine, rectal suppositories combining ergotamine with caffeine and an antispasmodic have proven most effective. In cluster headache, because of its transitory nature, the best results are usually obtained with ergotamine or dihydroergotamine used parenterally or by the aerosol inhalation of ergotamine. The use of antiemetics such as Compazine® (prochlorperazine) or Marezine® (cyclizine hydrochloride) is very helpful in the prevention of nausea caused by the drug and headache.

The importance of administering the medication early in the course of an attack, and giving it in adequate doses, cannot be overestimated. Many therapeutic failures are ascribable to too small a dosage given too late. Many errors in therapy are owing to lack of knowledge of how to use the drug—from undue fears of its danger on the one hand to recklessness in its administration on the other. However, the physiologic effects of ergot are exceedingly variable from person to person. Even in the same patient the way the body deals with the drug varies with certain physiologic states of the responding tissues. For example, the rate of disintegration of an ergotamine tablet—or even the rate at which the drug gains access to the circulation—is not necessarily compatible with the effectiveness of this chemical agent in the treatment of migraine. Although the site of action is both peripheral and central, little is known of the fate and excretion of ergot alkaloids. Furthermore, many of the side effects of ergotamine are probably referable to the central nervous system, and the route of administration would have little effect on them.

Because of its powerful vasoconstrictor action, ergotamine should not be used in patients who have or are suspected to have peripheral, cerebral or coronary vascular disease of venous or arterial origin. It is also contraindicated in patients with liver disease, renal damage, hypertension, pregnancy or septic states and in cachectic patients.

TABLE 1.—*Anti-Serotonin Activity in Vivo in Relation to Clinical Efficacy as Migraine Prophylaxis*

Compound	Inhibition of Serotonin-induced Edema in the Rat's Paw: E. D. 50 meg./kg.	Inhibition of Serotonin-induced Edema in the Rat's Paw: Relative Value*	Relative Clinical Effect (Range, 0 to 4+)
1. Hydergine	833	7	+
2. BOL 148†	196	29	+
3. Cyproheptadine	26	150	++
4. UML-491 (methysergide)	13	440	++++

*LSD-25 = 100.
†D-2-Brom-lysergic acid diethylamide tartrate

In the late stages of migraine attack, analgesic and sedatives are sometimes helpful if the headache has persisted long enough for the vessels to become firm and tortuous. In an occasional patient, relief is secured from an acute attack by inhalation of 100 per cent oxygen, by the administration of injectable Dramamine® (dimenhydrinate) or even by local infiltration of the affected artery by procaine. Efforts to abort "classical" migraine at the onset of aura by the use of nitroglycerin, carbon dioxide, nicotinic acid or other vasodilating agents have not been successful.

Prophylactic Treatment of Migraine

In appraisal of a prophylactic chemical agent in the treatment of migraine, it is well to note that we can be misled by the natural history of the disorder, particularly by the unpredictable remissions which can last for months or even years. Attempts to lessen the frequency of attacks of migraine in over 1600 patients by pharmacotherapy were made in previous studies.[9] The frequency and/or severity of the attacks was decreased significantly in over 50 per cent of the patients, with all categories of chemical agents used. These included sympatholytics, antispasmodics, sedatives, histamine, vasoconstrictors, vitamins and central nervous system stimulants, used alone or in combination. The results obtained with these drugs were not appreciably different from the results with placebos, which brought about a 45 per cent improvement.

Migraine patients may profit to a limited extent from the prophylactic use of tranquilizing drugs and in some instances may be especially helped by drugs such as methaminodiazepoxide (Librium®) and certain monoamine oxidase inhibitors that elevate the patient's mood.

Recently we at the Montefiore Hospital Headache Unit have been encouraged by our experience with 1-methyl-D-lysergic acid butanolamide (methysergide) (UML-491).[5,7] This substance is a serotonin antagonist, the basic actions of which are still to be

TABLE 2.—*Responses of Two Groups of Migraine Patients to Alternative Treatments*

	UML-491	Placebo	Totals
Excellent or good	97	8	105
Fair	30	7	37
Poor	23	12	35
Unreported	26	3	29
Totals	176	30	206

determined. Our experience indicates that the effectiveness of a drug in the treatment of migraine may be related to its ability to inhibit serotonin (Table 1). Recent evidence indicates that UML-491, in addition to its central and anti-inflammatory properties of a nonspecific nature, may secondarily induce peripheral vasoconstriction. It has been suggested that the vasoconstrictor effect is dependent upon the capacity of UML-491 to increase the sensitivity of the individual to his own vasoconstrictor substance. Such vasoconstriction, indirectly induced, is presumed to be the basis of therapeutic action which this agent possesses in the prevention of vascular headaches.[3] However, it should be noted that methylation of lysergic acid derivatives in position I not only increases serotonin antagonism but decreases all the other generally known pharmacodynamic properties of these compounds, including vasoconstriction. Whatever its specific action, in 16 months of use it has reduced the frequency and severity of headaches in 65 per cent of a group of 176 patients, which is significantly different from placebo response (Table 2). The average dose for patients with migraine in this series was 6 mg. daily, administered in 2 mg. doses spread out over the day.

Muscular Contraction Headache of Tension Type

Tension headaches occur in connection with constant or periodic emotional conflict, of which the patient is partially aware. They have no prodromata and are usually bilateral, commonly suboccipital but sometimes frontal or around the entire head as a band. There is a gradual onset of the head discomfort, which is frequently described as aching, pressing or tightness but may simulate organic pain of any type. Frequency, duration and severity are variable, but once a headache begins it usually persists for hours or even several days.[10]

Excessive muscle contraction and tender spots in the neck and scalp are physical features, and there also may be limited movement of the neck. Tension headache is not accompanied by neurological signs.

As can be demonstrated by action potentials electromyographically recorded from the muscles of the head and neck, sustained contraction of these muscles is associated with the pain.[11] However, pain of any etiologic background can cause muscle contraction, so that observing the presence of a muscle

TABLE 3.—*Muscle Tension Headache—Symptomatic Treatment*

Medication	Action	Per Cent Improved	No. of Patients
Dextropropoxyphene hydrochloride (Darvon)	Analgesic	58	120
Acetylsalicylic acid (aspirin)	Analgesic	55	120
Placebo		45	100

TABLE 4.—*Results with Various Agents in Treatment of Muscle Tension Headache*

Medication	Action	Per Cent Improved	No. of Patients
Aspirin	Analgesic	74	400
Phenacetin	Analgesic		
Caffeine	Stimulant		
Sandoptal (Fiorinal)	Sedative		
Dextropropoxyphene hydrochloride	Analgesic	69	262
Aspirin	Analgesic		
Phenaglycodol (Darvon compound)	Tranquilizer		
Placebo		45	100

spasm or recording it by electromyography does not prove a causal relationship. It has been assumed that ischemia which develops in the area of the contracted muscles may play a role in maintaining the pain. However, our measurements with radioactive sodium have indicated that the blood flow in the involved muscles may be actually increased. Further work is being done to prove or disprove this preliminary finding. Another factor may be a central spread of the excitatory effect of noxious stimulation of soft tissues of the neck. Whether one or more of these factors is responsible for the pain in muscle spasm is still to be determined.

Symptomatic Treatment of Tension Headache

As ordinarily used, the nonaddicting analgesics alone are seldom efficient in relieving an acute attack of tension headache. Likewise, tranquilizers and sedatives rarely control the discomfort. But when the analgesic is combined with a tranquilizer or sedative it is extremely effective, for in combination these drugs affect not only the pain threshold but also the reaction to pain (Tables 3 and 4). An analgesic combined with a sedative or a tranquilizer or both gives effective relief in over 70 per cent of treated cases, whereas nonnarcotic analgesics or sedatives, when used alone, are less effective (55 per cent).[6] It should be noted that placebos are effective in approximately 45 per cent of these patients.

The ideal analgesic for the treatment of tension headache should be effective at levels not impairing sensorium or vital functions, and it should be free of addicting properties, have negligible side effects or toxicity and be simple to administer.

Prophylactic Treatment of Tension Headache

Preventive treatment of tension headaches by chemical agents has undergone a change in recent years because of the introduction of tranquilizers, central muscle relaxants and related compounds. However, since tension headaches are frequently the result of psychological factors, therapy should not neglect this important area. Drugs cannot replace insight and help to the patient in understanding his emotional problems, but they are of value in reducing emotional tension and allowing the patient to handle stressful situations more effectively.

For purposes of evaluating their effectiveness, tranquilizers may be classified by their chemical structure into the following groups: the phenothiazines, the derivatives of rauwolfia, the diphenylmethanes, substituted propanediols, and methaminodiazepoxide.

All members of each chemical group share pharmacological properties and may differ from each other only by dosage requirements. The substances closely related in chemical structure are also likely to produce comparable clinical and toxic effects. Table 5 summarizes some of our experience with the use of tranquilizers in prophylactic treatment of tension headache.

A compound of another type that we have considered in the interval treatment of muscle tension headache is aminophenylpyridone (amphenidone) which has both tranquilizing and analgesic action. Appraisal of this drug in a recent study indicated it was an effective agent in 66 per cent of the patients.

Future Pathways

The necessity for developing new and more critical methods for assessing the effects and efficacy of new pharmacologic agents in the treatment of headache has been stressed by many investigators. It is the author's opinion that the future approach to the evaluation of such drugs must include chemical and pharmacological methods which will enable us to diagnose and classify headache by more objective means. Through these techniques, including the determination of blood levels of drugs, bioassays and the use of radioactive tracers and electronic methods, the subjective responses of patients can be evaluated by objective parameters. With these approaches in mind, the gulf between what the clinician observes and what the neurochemist and pharmacologist demonstrate should be more easily bridged.

TABLE 5.—*Results of Prophylactic Treatment of Muscular Tension Headache with Various Tranquilizer Agents*

	No. of Patients	Per Cent Improved
Methaminodiazepoxide (Librium®)	160	72
Meprobamate (Miltown®)	527	62
Phenaglycodol (Ultran®)	514	61
Hydroxyphenamate (Listica®)	66	60
Reserpine (Serpasil®)	641	55
Chlorpromazine HCl (Thorazine®)	114	54
Placebo	100	45

We have progressed a long way from Galen in our approach to pharmacological treatment of headache. It was Galen who said, "All who drink of this remedy recover in a short time, except those whom it does not help, who all die. Therefore, it is obvious that it fails only in incurable cases."

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